

II. RESPONSE

A. State of the Claims

Claims 38, 40, 52-61, 63-68, and 70-75 are currently pending. Claim 38 has been amended to more particularly claim the invention. Support for the amendment may be found throughout the specification and the sequence listing as filed. Claims 39 and 100 as filed list the amino acid sequences now recited within claim 38. Claims 39 and 100-103 have been cancelled. Applicants expressly do not disclaim the subject matter of claims 100-103 and expressly reserve the right to pursue claims to that subject matter.

Applicants respectfully request that the present amendment after final rejection be entered. The present amendment cancels claims 39 and 100-103 and amends claims 38 to incorporate the limitations of these claims. Applicants respectfully submit that the amendment places the claims in a better form for consideration on appeal by improving their clarity and reducing the number of claims and issues on appeal. 37 C.F.R. §1.116(b).

Support for the amendments may be found throughout the specification and in the claims as filed. For example, support may be found at page 4, lines 1-25, and in the section entitled “Assays for LPS responsiveness” on pages 87 and 88. The amendments introduce no new matter.

Appendix A to this response provides a marked copy of the amended claims. Appendix B to this response provides a clean copy of the pending claims for the convenience of the Examiner.

B. The Claims are Definite Under 35 U.S.C. § 112, Second Paragraph

Claims 38-40, 52-61, 63-68, 70-75, and 100 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite. Two grounds are asserted for this rejection: (i) that the term TLR-4 is

insufficiently defining of the TLR-4 polypeptides of the invention and (ii) that the phrase “lipopolysaccharide mediated response” is unclear. Applicants respectfully traverse both grounds of rejection.

i. Amended Claim 38 Must be Definite.

The Action maintains the rejection of claims 38-40, 52-61, 63-68, 70-75 and 100-103 on the grounds that “the name TLR-4 has not been defined in the claims and specification so as to allow the metes and bounds of the claims to be determined.” The Action at page 2, lines 10-11. Applicants respectfully traverse.

Applicants note that the asserted grounds for rejection, *i.e.* that the specification does not disclose the structure of TLR-4, cannot apply to claims 39, 57-61, 74 and 100. Claims 39, 57-61, 74 and 100 expressly recite either the amino acid sequences of several homologous TLR-4 polypeptides or the nucleotide sequences encoding those polypeptides. These claims necessarily recite the structure of TLR-4 polypeptides and therefore cannot be indefinite on the grounds asserted by the Action. Applicants note that claim 38 has been amended to recite these structures as listed in the presently cancelled claim 39 so that claims to commercially important subject matter may be allowed. Nevertheless, Applicants expressly do not admit that the term TLR-4 is indefinite as provided by the specification read in light of the knowledge and skill of the ordinary artisan.

ii. The Legal Standard under 35 U.S.C. § 112.

A proper evaluation of the claims under the second paragraph of 35 U.S.C. § 112 requires that the claims be read in light of the specification as interpreted by one of ordinary skill in the art. *North Am. Vaccine, Inc. v. American Cyanamid Co.*, 7 F.3d 1571, 1579, 28 USPQ2d 1333, 1339 (Fed. Cir. 1993); *In re Moore*, 439 F.2d 1232, 1235 (C.C.P.A. 1971). Furthermore, the law does not require that only immutable or invariant terms be used in claim language. Inventors are

encouraged to use concise language, as long as it is reasonably definite in view of the specification. This is long established law. *North Am. Vaccine, Inc.*, 7 F.3d 1571 at 1579; *Miles Lab., Inc. v. Shandon, Inc.*, 997 F.2d 870, 875, 27 USPQ2d 1123, 1126 (Fed. Cir. 1993); *Loom Co. v. Higgins*, 105 U.S. (Otto.) 580, 586 (1881).

iii. Applicants have defined the term TLR-4 in light of the specification and the skill of the ordinary artisan.

Applicants have provided a detailed and consistent definition of TLR-4 in the specification. Most particularly, TLR-4 as used by the Applicants in describing particular embodiments refers explicitly to polypeptides of the sequences of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:98 or SEQ ID NO:99 and those sequences at least about 85% similar thereto or biologically functional equivalents thereof. See the specification at page 30, lines 4-15 and page 73, line 18 through page 76, line 11, and Example 8, pages 105-122. In view of the properties and structures of TLR-4 polypeptides thus supplied in the present specification Applicants submit that the specification sheds sufficient light upon the present claims to render them clear and definite to one of skill in the art under the second paragraph of 35 U.S.C. § 112.

Applicants also point out that the law does not require that the Applicants define in the specification every term of art well known to the artisan. Use of a well known term of art in the specification without detailed definitions thereof does not render claims utilizing that same language indefinite. *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1556-58, 220 USPQ 303, 315-16 (Fed. Cir. 1983). Claims may therefore make use of the language understood by those of skill in the art without additional, detailed definitions in the written description. *Id.* Where later developed terms are arguably more definite than the terms available near the filing date, later accepted and more precise terms are favored. *In re Fisher*, 427 F.2d 833, 838 (C.C.P.A. 1970). The name TLR-4 is in common use among artisans in the field in exactly the

sense in which the Applicants have defined it. Although the referenced polypeptide may have once been named Toll-4, use of the more current and more current and precise term TLR-4 (or TLR4) cannot render the claims indefinite. *In re Fisher* at 838.

Indeed, the identity of TLR-4 within the family of Toll-like receptors is unambiguous, as is known to those of skill in the art. Applicants have provided numerous factual exhibits of the knowledge and skill in the art with respect to the definition of TLR-4 polypeptides. These factual exhibits include examples of the scientific literature display the knowledge available to one of skill in the art to define and recognize TLR-4 polypeptides. The factual evidence also includes the declaration of Dr. David D. Chaplin, which states that the specification as filed provides sufficient structural and functional properties by which to identify a protein as TLR-4 or its homolog. Applicants point out that these facts should not be lightly dismissed absent any showing of a factual or scientific basis to doubt their veracity.

Applicants submit, that in view of the above, one of ordinary skill in the art would find the language of the claims prior to amendment definite in light of the specification. In any event, Applicants contend that the present claims, which recite specific sequences, are definite under the second paragraph of 35 U.S.C. § 112.

iv. The term “Lipopolysaccharide mediated response” is clear, definite, and well known to those of skill in the art.

Claims 38, 40, 52 and 101-103 are rejected on the grounds that they are indefinite because the phrase “lipopolysaccharide mediated response” is allegedly not clear. The Action queries “where does the lipopolysaccharide pathway begin and end?” The Action, page 3, lines 11-12. Applicants respectfully traverse.

a) Lipopolysaccharide mediated responses have been well known to the artisan for decades.

In response to the repeated query, "Where does the lipopolysaccharide pathway begin and end?" Applicants point out that, as is well known to the ordinary artisan, responses to the presence of endotoxin (LPS) occur at the subcellular, cellular, tissue and organismal levels. Indeed, in the most extreme example of the "beginning and end" of the "LPS pathway," Applicants draw attention to the passages beginning at line 19 of page 2 and extending through line 5 of page 3. For convenience, Applicants reproduce those passages here (emphasis added):

...An important case in point concerns Gram-negative bacteria, all of which bear endotoxin (lipopolysaccharide, LPS) molecules in their outer membrane, which trigger a strong immune response on the part of the host which produces a shock-like syndrome, characterized by low blood pressure and hyporeactivity to vasoconstrictor agents.

When macrophages are exposed to pure preparations of endotoxin, they secrete numerous cytokine mediators, including tumor necrosis factor (TNF, TNF α), interleukin-1 (IL-1), interferon- α/β , GM/CSF, IL-8 and ultimately smaller "autocoid" molecules, all of which mediate an intense inflammatory reaction. Endotoxin recognition acts as an early warning signal through which a host may mount a timely defense against invasion by Gram-negative organisms. However, widespread activation of macrophages by endotoxin results in the development of septic shock. By most estimates, Gram-negative septic shock is responsible for 100,000 deaths per year in the United States alone. The entire syndrome of hypotension, coagulopathy, pulmonary edema and acute renal failure results, in large part, from the release TNF and other cytokines in response to exposure to endotoxin.

Clearly, Applicants do not advocate the exposure of patients to LPS as an embodiment of the claimed methods for screening for LPS mediated responses. However, it does remain possible to measure such responses at the organismal level in experimental organisms such as mice. To wit (emphasis added):

Thirty years ago, mice of the C3H/HeJ strain were noted to be specifically and globally unresponsive to endotoxin, while closely related animals of the C3H/HeN or C3H/OuJ substrains exhibited normal responses (Sultz, 1968). The median lethal dose of endotoxin is more than 100-fold higher in C3H/HeJ mice than in either of these other strains. Macrophages of C3H/HeJ mice fail to

produce cytokines in response to endotoxin, and B-lymphocytes of C3H/HeJ mice are not driven to proliferate by endotoxin. While C3H/HeJ mice are highly resistant to the lethal effect of endotoxin, they are unusually sensitive to infection by gram-negative organisms. The mean lethal inoculum with *Salmonella typhimurium*, for example, is two organisms in C3H/HeJ mice, whereas several thousand organisms are required to kill mice of the C3H/HeN strain.

As Applicants have well documented in the specification, they have disclosed that the single gene that underlies this sensitivity or resistance to exposure to endotoxin encodes TLR-4 and that TLR-4 is *the* LPS receptor. TLR-4 is indispensable to the signaling that results in the LPS mediated responses. Thus, modulation of native TLR-4 activity in the cellular response to LPS necessarily modulates the LPS response. Therefore, through the application of a putative modulator of TLR-4 signaling (as provided by the Applicants), one may determine if the particular LPS response has, in fact, been modulated in the above example by observing whether the mouse lives or dies. In this particular, albeit extreme embodiment, Applicants are at a loss to know how it can be uncertain or unclear just exactly what responses may be expected to be manifest after exposure to LPS.

b) The Action misquotes Dr. Chaplin in asserting grounds for rejection.

In response to the assertions in the Action (page 5, lines 5 and 6) that Applicants have disclosed “some of the ‘actors and elements of lipopolysaccharide mediated response,’” (emphasis added) Applicants point out that the declaration of Dr. Chaplin has been misquoted. The proper quote reads “The specification clearly sets for the actors and elements of lipopolysaccharide mediated responses that are mediated by TLR-4.” Declaration of Dr. Chaplin, paragraph 5 (emphasis added).

No ambiguity exists in the statement of the declaration. Rather, the ambiguity has been introduced by the Action’s misquotation, which replaces Dr. Chaplin’s “the actors” with the Action’s “some actors.” Since there is no basis provided for so modifying Dr. Chaplin’s

statement, any rejection based upon this misstatement of fact must be in error. Applicants request that any rejection based upon this misquotation be withdrawn.

c) The Action mischaracterizes Applicants' disclosure in asserting grounds for rejection.

The Action quotes the specification out of context in order to impugn the clarity and importance of Applicants' discovery and the claimed invention. The Action cites the last paragraph of page 3, but only quotes a single sentence. For convenience and accuracy, Applicants herein reproduce the entirety of the cited paragraph (quoted passage in italics):

Endotoxin is known to trigger both tyrosine and serine phosphorylation events within the macrophage cell, and at least in part, *ras*, *raf*, *MEK*, and members of the MAP kinase family are also involved in signal transduction (Geppert *et al.*, 1994). The endpoints of endotoxin signaling include activation of the transcription of TNF and various genes, and activation of the translation of TNF mRNA (Beutler *et al.*, 1986; Han *et al.*, 1990). At the protein level, this stimulation by endotoxin leads to a several thousand-fold augmentation of cytokine biosynthesis by a macrophage cell. But the initial controlling element and event in the signaling pathway of macrophage response to endotoxin has not been identified. *Thus, in spite of its importance, most of the endotoxin signaling pathway remains relatively unknown.* Recently however, the Toll-like receptor 2 (TLR2) has been suggested to partially mediate lipopolysaccharide-induced cellular signaling (Gerard, 1998; Yang *et al.*, 1998).

In the context of the full paragraph it is clear that the quoted statement refers to the impediment to research imposed by the lack of identification of the "initial controlling element" in the pathway of macrophage response to endotoxin (LPS). Indeed, this paragraph occurs in the description of related art and describes the state of the art *prior* to the disclosure by the Applicants of the *Lps* gene, *i.e.* TLR-4. Moreover, it is the signaling pathway, at which TLR-4 is at the core, that was unknown, not LPS mediated responses, which have been known to those in the art for decades (see above). And further, Applicants' specification discloses the key actor at the core of LPS mediated responses, TLR-4.

d) Misquotation and Mischaracterization do not render the claims indefinite.

The mischaracterization of the state of the art and the misquotation cited above cannot rise to the task of demonstrating that the present claims are indefinite for reciting a “lipopolysaccharide mediated response.” Indeed, given the mature state of the art relevant to lipopolysaccharide mediated responses, the ordinary artisan would immediately understand the nature and scope of the claimed methods.

e) The Term “Lipopolysaccharide mediated response” has an established meaning in the art.

Applicants emphatically reiterate that the law does not require that the Applicants define in the specification every term of art well known to the artisan. Use of a well known term of art in the specification without detailed definitions thereof does not render claims utilizing that same language indefinite. *W.L. Gore & Assoc., Inc.* 721 F.2d 1540, 1556-58. If necessary, a standard reference work may inform the reading of the specification, and if so, that in itself does not render claims utilizing that language indefinite. *Atmel Corp. v. Information Storage Devices, Inc.*, 198 F.3d 1374, 1382 (Fed. Cir. 1999) (“...even a dictionary or other documentary source may be resorted to...”).

Indeed, the content of such a standard reference work is intrinsic evidence of the meaning of claim terms. The governing court of U.S. patent law has said:

Dictionaries, encyclopedias and treatises, publicly available at the time the patent is issued, are objective resources that serve as reliable sources of information on the established meanings that would have been attributed to the terms of the claims by those of skill in the art. Such references are unbiased reflections of common understanding not influenced by expert testimony or events subsequent to the fixing of the intrinsic record by the grant of the patent, not colored by the motives of the parties, and not inspired by litigation. Indeed, these materials may be the most meaningful sources of information to aid judges in better understanding both the technology and the terminology used by those skilled in the art to describe the technology.

Texas Digital Sys., Inc. v. Telegenix Inc., 308 F.3d 1193, 1202-3 (Fed. Cir. 2002).

Applicants have already supplied passages from the reference work “Medical Microbiology, 4th Ed.” S. Baron, ed., 1996, University of Texas Medical Branch at Galveston, Galveston, TX., pages 130-133.¹ Although published prior to the date of issue of the present claims, it nevertheless satisfies the Court’s concerns and is an example of a standard reference work or treatise that verifies that a lipopolysaccharide mediated response is well understood by those of skill in the art. The passages are a mere summary of the extensive literature in the field of endotoxin biology as it existed in 1996, but nevertheless serve to demonstrate that one of skill in the art would know the metes and bounds of a LPS mediated response. As indicated in the Applicants’ specification at page 2, line 20, and as is well known and readily apparent to one of skill in the art, lipopolysaccharide is a term synonymous with endotoxin (see Medical Microbiology at page 130, column 2, 4th paragraph, under the heading “Structure of Endotoxin”).

Further, and as is well known and readily apparent to one of skill in the art, “The biologic effects of endotoxin [LPS] have been extensively studied” Medical Microbiology at page 131, column 1, under heading “Biologic Activity of Endotoxin.” Thus, LPS mediated responses at least include (as of 1996) those activities listed in Table 7-4, page 132 of Medical Microbiology. Indeed, the central importance of LPS in the mediation of cellular responses to a variety of conditions is clear and well known to the ordinary artisan.

At the time of this summary (1996), the specific mechanism of cellular response was not clear. See Medical Microbiology at page 132, bottom of column 1, extending to the top of column 2. What was clear was that the host cell exposure to endotoxin was key to the “myriad

¹ Appendix D to Applicants’ previous response to the Office Action of April 23, 2002, filed September 23, 2002.

sequelae" that exposure to endotoxin produces. "It does seem clear that the host cellular response to endotoxin, rather than a direct toxic effect of endotoxin, plays the major role in causing tissue damage." Medical Microbiology, page 132, top of column 2. Indeed, it is the Applicants' discovery that TLR-4 polypeptide plays the key role as a cell's LPS receptor and is, therefore the key in the pathway leading to the various responses to certain types of infection. "[T]he demonstration that *Lps* is identical to TLR-4 leaves no room for doubt that TLR-4 is essential for LPS signalling." The specification at page 104, lines 14-15. This discovery therefore identifies *the* pathway, *i.e.* through TLR-4, by which these responses are mounted.

v. Summary

The clarity that Applicants' discovery provides is engendered in the terms of the claims. Thus, the methods require "obtaining a cell expressing a TLR-4 polypeptide," "providing to the cell LPS sufficient to induce a LPS mediated response" and "measuring a lipopolysaccharide mediated response mediated by the TLR-4 polypeptide." See claim 38. The Applicants' specification provides explicit means by which one may measure a LPS response mediated by the TLR-4 polypeptide and the skill of the art provides even more.

Applicants submit that the claims are definite under the second paragraph of 35 U.S.C. § 112 when properly viewed in light of the ordinary skill of one in the relevant art and the detailed descriptions available to the artisan in the applicants specification. Applicants therefore respectfully request that the rejections be withdrawn.

C. The Pending Claims are Enabled.

The Action again rejects claims 38-40, 52-61, 63-68, 70-75 and 100-103 under the first paragraph of 35 U.S.C. § 112. The Action alleges that the only screening method enabled is that which results in the altered expression of TLR-4 of SEQ ID NOS: 2, 4, 6, 98, or 99. Therefore,

the Action concludes, methods of screening for modulators of LPS mediated responses through their interaction with TLR-4 are not enabled. Applicants respectfully traverse.

i. The Legal Standard of Enablement

To be enabling within the meaning of 35 U.S.C. § 112, the application must contain a description sufficient to enable one skilled in the art to make and use the claimed invention without unduly extensive experimentation. *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984). Furthermore, it is well settled that the examiner has the initial burden of producing reasons that substantiate a rejection based on lack of enablement. See *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971); *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). The examiner's burden requires that the examiner supply a factual basis or scientific principle to reasonably doubt the accuracy of a clear disclosure *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971).

ii. The Action supplies no factual or scientific principle to reasonably doubt Applicants' disclosure.

Applicants contend that the Action has not carried the burden of establishing a *prima facie* case of lack of enablement. To the contrary, in maintaining the rejection, The Action demands unnecessary claim limitations or posits a number of factually unsupportable allegations regarding the nature and function of the claimed methods and TLR-4 in particular.

iii. The Action misconstrues the invention in asserting lack of enablement.

The Action demands that the method disclose "how the modulator targets a TLR-4 polypeptide and if the response being measured is in fact a lipopolysaccharide mediated response, since there is [sic] no controls to compare the results to." The Action at page 7, lines 14-16.

Applicants point out that the pending claims are directed to methods of *screening* for modulators of a lipopolysaccharide mediated response that compare the response before and after contact of TLR-4 with a *putative* modulator or *candidate* substance. As such, the method does not require that the exact mode of action of any successful modulator so identified be determined *prior* to the screening procedure, as the Action demands. Indeed, if the artisan knew the identity of the modulator and its mode of action, there would be no need to practice the present invention. The present invention is directed to methods of identifying such modulators, whose identity would, of course, be unknown absent the present invention.

Furthermore, the nature and scope of a lipopolysaccharide mediated response is, as presented above, clear to the artisan, as presented in section B, above. The assertion that there "is no controls [sic]" ignores the limitations of the claims, which specify the comparison between the measured LPS response *prior* to the contact with TLR-4 by the modulator with the measured LPS response *after* contact with TLR-4 by the putative modulator, wherein a difference in the lipopolysaccharide mediated responses indicates that the putative modulator is a modulator of a lipopolysaccharide mediated response. See claim 38.

Applicants are at a loss to understand the alleged deficiency in the enablement of the claimed methods.

iv. Unsupported, or unsupportable allegations do not rise to the level of factual evidence or scientific principle.

Additionally, the allegation that the LPS mediated response mediated by TLR-4 could be due to some other pathway (the Action at page 7, line 18) simply ignores the nature of Applicants' discoveries and the extensive disclosure provided regarding the central, indispensable role of TLR-4 polypeptides in LPS mediated responses. The Action cites no reference, nor supplies any Examiner's affidavit. Indeed, the Action supplies no factual basis at

all for doubting the veracity of Applicants' discovery and disclosure. In fact, the general acceptance and importance of Applicants' discovery to those in the art is reflected in the extensive literature already made of record in the present application, and which refers to and builds upon Applicants' work. The central role of TLR-4 in the signaling pathway is now widely accepted by the field. Applicants have made of record publications acknowledging Applicants' discovery and the role of TLR-4 in LPS responses. For example, see Applicants Appendix E to their response filed September 23, 2002, which contains a recent paper in the widely respected journal *Nature*.

v. Applicants supply abundant factual evidence of enablement.

In response to the previous argument in rejection, Applicants have referred to the specification at page 2, line 14 through page 4, line 24, and especially page 22 lines 3-7 for a succinct description of the events and circumstances that comprise the induction of a response to LPS and the resultant responses that may be measured as indicative of an LPS mediated response. Further, exemplary parameters and methods for measuring and determining the LPS mediated responses are found in several locations in the specification: page 87, line 5 through page 88, line 15, Example 2 (page 95, line 25 through page 96, line 18), and Example 9 (page 123, line 1 through page 129, line 20). All of these responses may be utilized in the practice of the presently claimed methods by those of skill in the art, and the choice of which to use is a matter of preference and circumstance. And, in any event, all are well recognized by those of skill in the art as a "lipopolysaccharide mediated response" as evidenced by the numerous factual materials, including the declaration of Dr. Chaplin, made of record in this application.

In addition, the specification provides specific examples of how to measure the LPS mediated response mediated by TLR-4. In the section of the Specification titled "Assays for LPS responsiveness" two common examples of LPS-mediated response assays are described: a

splenocyte proliferation assay and a macrophage response assay. See the specification at page 87, line 8 to page 88, line 15. The splenocyte response assay compares the proliferation of splenocytes incorporating tritiated thymidine (as measured by counts per minute, CPM) with and without stimulation with LPS. The macrophage response assay measures the per cent of cytotoxicity due to TNF released by cells in response to LPS. In yet another means of assaying for LPS response, TNF production may be directly measured. See the specification at page 3, lines 7-13, FIG. 15C, and page 87, line 23 through page 88, line 7. As described above and elsewhere in the specification, TNF production or secretion is one of the most salient and available LPS mediated responses available to the artisan.

These are exemplary parameters and methods for measuring the LPS response. Further, and in direct contradiction to the assertions made in the Action, claims 63 and 64 expressly recite TNF secretion as one LPS inducible response that may be measured. Therefore, the specification and the claims as filed provide concrete examples, methods, and standards for measuring responses induced by LPS endotoxin mediated through TLR-4. See paragraph 15 of the Chaplin declaration, which provides verification of this fact by one of skill in the art.

vi. Applicants' factual evidence remains unrefuted.

Applicants have repeatedly, and respectfully, called attention to these passages, which describe and demonstrate specific LPS mediated responses that may be measured in the implementation of the present invention that are well known to the artisan. Applicants again now again point to this body of factual evidence and point out that it remains unrefuted by any fact or scientific theory cited by this or any previous Action. In the absence of any factual basis or scientific principle sufficient to doubt the substantial body of factual and scientific evidence demonstrating that the ordinary artisan may make and use the claimed invention without undue experimentation, Applicants submit that the present claims are enabled under 35 U.S.C. §112.

Nowhere has the Action produced factual evidence or scientific principle to doubt the accuracy of Applicants' disclosure. The Action instead suggests that which is not known or accepted by the relevant artisan. For example, in the absence of any factual basis upon which to doubt the central, indispensable role of TLR-4 in LPS mediated responses, the Action asserts that "some other pathway" could be responsible. Applicants respectfully submit that this statement is unsupported and unsupportable. Since the present rejection is based upon this errant assertion and the unnecessary claim elements suggested above, Applicants respectfully request withdrawal of the rejections.

vii. The Action misconstrues the invention and Applicants' arguments.

The Action maintains that there is but a single embodiment of the present invention that is enabled: the induction of TLR-4 expression that may result from LPS presentation to cells. But, as previously explained, although altered expression of TLR-4 of SEQ ID NOS: 2, 4, 6, 98, or 99 (or a reporter gene, see claim 40) may be *one* mode of LPS response that is measured, it is not the sole means of measuring TLR-4 mediated LPS responses disclosed by the specification.

With regards to this issue, Applicants respectfully note that the Action continues to misconstrue Applicants arguments submitted in previous responses. In particular, the present Action states "Applicant [sic] argues LPS response disclosed by the specification is by far not the sole means of modulating the TLR-4 response." The Action at page 7, lines 10-12. Applicants note that this statement confuses the LPS mediated response and the role of putative or identified modulators of TLR-4's role in the response. The statement appears to equate LPS responses with modulators of TLR-4. But, as is readily apparent to those of skill in the art, this assertion is simply incorrect in view of the specification and the relevant literature of the art.

The specification and the arguments presented by Applicants in previous responses make clear that *TLR-4 is the LPS receptor*. TLR-4 is the key component of the signaling pathway that

results in, for example, an increase TNF production as a result of lipopolysaccharide exposure to cell surface receptors and other, well known LPS responses (including death, as discussed above). See, for example, the specification at page 123, line 1 through page 129, line 20. The LPS response is, therefore, largely “downstream” of the action of TLR-4 polypeptides at the cell surface. Modulation of LPS response through the modulation of TLR-4 activity, not merely its expression, is described and enabled by the specification as understood by those of skill in the art.

The Action nevertheless demands that “For the person of ordinary skill in the art to screen for modulators of LPS mediated response by any other means that those disclosed as ‘enabling’ above [referring to up-regulation of TLR-4 expression], the artisan must first isolate other proteins capable of direct or indirect interaction with LPS and its modulators, and develop screening assays to determine if certain compounds can be modulators of the LPS mediated response.” The Action at page 8, lines 13-17.

Applicants are simply at a loss to understand where the requirement for isolation of “other proteins capable of direct or indirect interaction with LPS and its modulators” is to be found in the art or the disclosure of the specification. If the Action intends to refer to previous arguments of the Applicants, which noted that the sensitivity of the LPS mediated response may be directly effected by the endogenous levels of TLR-4 expression, but that the LPS response itself may also be modulated by the nature of the physical interactions of TLR-4 with the other components of the pathway, Applicants respectfully point out that the mention of known modulators of TLR-4 sensitivity was provided to illustrate that the action of TLR-4 in initiating LPS mediated responses was not dependent upon the up-regulation or down-regulation of its expression.

Modulation of LPS response may occur through the modulation of TLR-4 activity, not merely TLR-4 expression levels. This core concept demonstrates the enablement of the present invention, which provides that further, additional modulators may be identified using the claimed methods of screening. With regards to any need to “develop screening assays to determine if certain compounds can be modulators of the LPS mediated response” Applicants respectfully note that this is exactly the problem solved by the presently claimed methods. Again, there is no need to *a priori* identify modulators in order to practice a method that acts to identify such modulators.

viii. Summary

The Action provides no factual basis or scientific principle upon which any doubt may be cast on the specification and the knowledge of those of skill in the art. The Action’s unsupported allegations do not address the objective enablement provided by the specification and cannot carry the heavy burden placed upon the Examiner. Therefore, Applicants respectfully submit that the Examiner has not carried the burden of establishing a *prima facie* case of lack of enablement. See *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971); *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). In view of the disclosure provided in the specification and the arguments provided above, Applicants request that the rejection be withdrawn.

D. Conclusion

Applicants have submitted remarks which are believed to place the present claims in condition for allowance. Should the Examiner have any comments or questions with regard to any statements contained herein the Examiner is respectfully requested to contact the Applicants’ representative listed below.

Please date-stamp and return the enclosed postcard evidencing receipt of these materials.

Respectfully submitted,



Thomas M. Boyce
Reg. No. 43,508
Attorney for Applicants

FULBRIGHT & JAWORSKI
600 Congress Ave., Suite 2400
Austin, TX 78701
(512) 536-3043

Date: February 13, 2003
